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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : <b>A61K 31/52 // (A61K 31/52, 31:19)</b>	<b>A1</b>	(11) International Publication Number: <b>WO 95/07079</b> (43) International Publication Date: <b>16 March 1995 (16.03.95)</b>
(21) International Application Number: <b>PCT/US94/09582</b> (22) International Filing Date: <b>24 August 1994 (24.08.94)</b> (30) Priority Data: <b>08/117,389</b> <b>7 September 1993 (07.09.93)</b> <b>US</b> (71) Applicant: <b>THE PROCTER &amp; GAMBLE COMPANY</b> <b>[US/US]; One Procter &amp; Gamble Plaza, Cincinnati, OH</b> <b>45202 (US).</b> (72) Inventor: <b>MITRA, Sekhar; 7305 Demar Road, Cincinnati, OH</b> <b>45243 (US).</b> (74) Agents: <b>REED, T., David et al.; The Procter &amp; Gamble</b> <b>Company, 5299 Spring Grove Avenue, Cincinnati, OH</b> <b>45217 (US).</b>	(81) Designated States: <b>AU, BR, CA, CN, JP, PL, RU, European</b> <b>patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU,</b> <b>MC, NL, PT, SE).</b> Published <i>With international search report.</i>	

(54) Title: COMPOSITIONS CONTAINING AN AMINO ACID SALT OF PROPIONIC ACID NON-STEROIDAL ANTI-INFLAMMATORY AGENTS AND CAFFEINE

## (57) Abstract

Compositions and methods for providing improved analgesic and/or anti-inflammatory effect by administering a safe and effective amount of a composition comprising certain amino acid salts of propionic acid non-steroidal anti-inflammatory agents along with an amount of caffeine sufficient to hasten the onset.

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COMPOSITIONS CONTAINING AN AMINO ACID SALT OF PROPIONIC ACID NON-STEROIDAL  
ANTI-INFLAMMATORY AGENTS AND CAFFEINE

TECHNICAL FIELD

5       The present invention relates to compositions and methods for providing improved analgesic and/or anti-inflammatory effect by administering a safe and effective amount of a composition comprising certain amino acid salts of propionic acid non-steroidal anti-inflammatory agents along with an amount of caffeine sufficient to hasten the onset.

10       BACKGROUND OF THE INVENTION

Inflammation, or the "inflammatory response", is the result of complex interconnected physiological events, including increased vascular permeability, fluid accumulations, and the migration of a changing population of inflammatory cells into the inflamed area. The clinical manifestations of inflammation include swelling  
15 (edema), increased local temperature, erythema, and pain. The inflammatory response can be triggered by any of a number of causative factors, including certain bacteria, radiation, hypersensitivity to chemical agents, arthritis-like conditions, and the like. The inflammatory response is generally believed to be a primary defense mechanism in the body, but, unchecked, can become excessive and can result in  
20 functional impairment.

The use of non-steroidal anti-inflammatory, anti-pyretic and analgesic drugs, especially the salicylates, which include aspirin and aspirin derivatives, to combat inflammation and attendant pain is accepted medical practice. The non-steroidals are commonly employed to relieve pain and inflammation associated with, for  
25 example, bursitis, arthritis, and the like.

While pain is incapable of precise definition due to its basically subjective nature, it can generally be said that the term refers to feelings of distress or suffering caused by stimulation of specialized nerve endings. A great variety of drugs have been developed to reduce pain in man and other animals; some directed to  
30 eliminating pain at its source, and others directed to blocking the perception of pain by the brain. Among the latter group of drugs that are designed to block the sensation of pain, are the analgesics, which generally relieve pain without causing unconsciousness. Analgesics can be further classified into two main categories: opioid analgesics, including morphine, codeine, levorphanol, and the morphine-like  
35 analgesics meperidine, and methadone; and antipyretic analgesics, such as aspirin, ibuprofen, phenacetin, acetaminophen, phenylbutazone, and indomethacin.

Although the precise pharmacological action of these analgesics is uncertain, there are certain effects which readily distinguish the opioid analgesics from the antipyretics. In particular, the antipyretics are weak analgesics, with much of their effect in the peripheral nervous system, so that behavioral changes do not usually occur. Generally, these analgesics relieve only pain originating from muscles, joints, tendons and fasciae, and are ineffective against deep visceral pain. However, the opioid analgesics are quite effective against all types of pain, with broad-based action in the central nervous system. Aside from potent analgesia, the opioids, also known as narcotics, often produce effects on mood and other behavioral changes. Perhaps the most notable side effect of opioid analgesics is the fact that their repeated use is associated with tolerance, as well as psychic and physical dependence.

The ornithine, lysine and arginine salts of ibuprofen useful for providing relief from pain and inflammation have been disclosed in, for example, U.S. 4,279,926 to Bruzzese et al., issued July 21, 1981. A process for the preparation of ibuprofen lysine tablets has been disclosed in EP 505,180, published March 19, 1992.

The use of the racemic mixture of ibuprofen together with caffeine has been disclosed in, for example, in U.S. Patent 4,464,376 to Sunshine et al. issued August 7, 1984. The use of ibuprofen, as well as other of the newer non-steroidal anti-inflammatory agents (i.e., excluding aspirin, acetaminophen and phenacetin) in the preparation of cough/cold pharmaceutical compositions containing sympathomimetic amines, has been disclosed in, for example, U.S. Patent 4,552,899 to Sunshine et al. issued November 12, 1985. The use of the S(+) form of ibuprofen has been disclosed in, for example, U.S. Patent 4,851,444 to Sunshine et al. issued July 25, 1989 and in combination with antihistamines in WO 9,205,783 to Gates et al. published April 16, 1992.

The present inventors have found that selected compositions comprising certain amino acid salts of the propionic acid NSAIDs in combination with caffeine provides further improved analgesic and/or anti-inflammatory effect.

It is therefore an object of the present invention to provide such compositions and methods for the treatment of pain and/or inflammation.

#### SUMMARY OF THE INVENTION

The present invention relates to a method of eliciting a sustained, enhanced analgesic response in a human or lower animal in need of such treatment, comprising administering to such human or lower animal a safe and effective amount of a composition comprising:

a. an analgesically and anti-inflammatory effective amount of an amino acid salt of a propionic acid NSAID; and

b. an amount of caffeine sufficient to hasten the onset of and enhance the analgesic response.

5 All percentages and ratios used herein are by weight unless otherwise indicated.

### DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to compositions and methods of eliciting a sustained, enhanced analgesic response in a human or lower animal in need of such  
10 treatment, comprising administering to such human or lower animal a safe and effective amount of a composition comprising ibuprofen lysinate, and an amount of caffeine sufficient to hasten the onset of and enhance the analgesic response.

The term "amino acid salt" refers to salts derived from pharmaceutically acceptable organic non-toxic bases of primary, secondary, tertiary and quaternary  
15 amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as triethylamine, tripropylamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, lysine, ornithine, arginine, histidine, caffeine, procaine, N-ethylpiperidine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglycamine, theobromine, purines, piperazine,  
20 piperidine, polyamine resins and the like.

The propionic acid derivatives of the non-steroidal anti-inflammatory agents which are useful in the compositions of the present invention are well-known to those skilled in the art and are disclosed in, for example, U.S. Patent 4,552,899 to Sunshine et al., issued November 12, 1985, incorporated by reference herein. For  
25 detailed disclosure of the chemical structure, synthesis, side effects, etc., of non-steroidal anti-inflammatory agents, reference may be had to standard texts, including Anti-inflammatory and Anti-Rheumatic Drugs, K. D. Rainsford, Vol. I-III, CRC Press, Boca Raton, (1985), and Anti-inflammatory Agents. Chemistry and Pharmacology, 1, R. A. Scherrer, et al., Academic Press, New York (1974), both of  
30 which are incorporated by reference herein.

The preferred non-steroidal anti-inflammatory agents useful in the composition of the present invention include the amino acid salts of the propionic acid derivatives such as ibuprofen, naproxen, benoxaprofen, flurbiprofen, ketoprofen, fenoprofen, fenbufen, indoprofen, piroprofen, carprofen, oxaprozin, pranoprofen,  
35 miroprofen, tioxaprofen, suprofen, alminoprofen, and tiaprofenic. Mixtures of these non-steroidal anti-inflammatory agents may also be employed. Of these propionic acid NSAIDs, ibuprofen, naproxen, and ketoprofen are most preferred.

Most preferred for use herein is the S(+) isomer of these NSAID salts. The term "S(+)" as applied to the analgesic agents herein is intended to encompass the dextrorotatory or S(+) isomer of the amino acid salt derivatives thereof. The expression "substantially free of the R(-) antipode" as used in conjunction with the term "S(+)" means that the S(+) enantiomer is sufficiently free of its R(-) antipode to exert the desired onset-hastened and enhanced analgesic effect. Practically speaking, this means that the active ingredient should contain at least 90% by weight of the S(+) enantiomer and 10% or less weight R(-) enantiomer. Preferably, the weight ratio of S(+) enantiomer to R(-) enantiomer is greater than 20:1, more preferably greater than 97:3. Most preferably the S(+) enantiomer is 99 or more % by weight free of R(-) enantiomer, i.e., the weight ratio of S to R is approximately equal to or greater than 99:1.

The safe and effective amount of the amino acid salts of ibuprofen, naproxen, benoxaprofen, flurbiprofen, ketoprofen, fenoprofen, fenbufen, indoprofen, pirprofen, carprofen, oxaprozin, pranoprofen, miroprofen, tioprofen, suprofen, alminoprofen, and tiaprofenic generally ranges from about 7.5 mg. to about 1000 mg., and are generally the same as their acid derivatives counterparts. Useful dosage of these agents can be found in The Physicians' Desk Reference, 47th Edition (1993) and in U.S. Patent 4,552,899 to Sunshine et al., issued November 12, 1985, both of which are incorporated by reference herein.

For example, the safe and effective amount of the amino acid salt of ibuprofen used in the compositions of the present invention generally ranges from about 50 to about 800 mg, preferably from about 50 to about 400 mg, more preferably from about 50 to about 200 mg and most preferably from about 50 to about 100 mg. The safe and effective amount of the amino acid salt of flurbiprofen used in the compositions of the present invention generally ranges from about 12.5 to about 300 mg, preferably from about 12.5 to about 200 mg, more preferably from about 12.5 to about 100 mg and most preferably from about 12.5 to about 50 mg. The safe and effective amount of the amino acid salt of ketoprofen useful in the compositions of the present invention generally ranges from about 5 to about 100 mg, preferably from about 5 to about 75 mg, more preferably from about 5 to about 50 mg and most preferably from about 5 to about 25 mg. Generally, the amount of the S(+) isomers of these agents will be about half of the amount of the racemic mixture.

Preferably, the pharmaceutical compositions of the present invention comprise the analgesic agent and caffeine in a ratio of from about 10:1 to about

1:10, preferably from about 5:1 to about 1:5 and most preferably from about 2:1 to about 1:5.

Various oral dosage forms can be used, including such solid forms as tablets, gelcaps capsules, granules, lozenges and bulk powders and liquid forms such as syrups and suspensions. These oral forms comprise a safe and effective amount, usually at least about 5% of the active component. Solid oral dosage forms preferably contain from about 5% to about 95%, more preferably from about 10% to about 95%, and most preferably from about 25% to about 95% of the active component. Liquid oral dosage forms preferably contain from about 1% to about 50% and more preferably from about 1% to about 25% and most preferably from about 3% to about 10% of the active component.

Tablets can be compressed, tablet triturates, enteric-coated, sugar-coated, film-coated or multiple compressed, containing suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, preservatives and flow-inducing agents.

Liquid oral dosage forms include aqueous and nonaqueous solutions, emulsions, suspensions, and solutions and/or suspensions reconstituted from non-effervescent granules, containing suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, taste-masking agents, coloring agents, and flavoring agents. Specific examples of pharmaceutically acceptable carriers and excipients that may be used to formulate oral dosage forms, are described in U.S. Patent 3,903,297, Robert, issued September 2, 1975, incorporated by reference herein. Techniques and compositions for making solid oral dosage forms are described in Marshall, "Solid Oral Dosage Forms," Modern Pharmaceutics, Vol. 7, (Banker and Rhodes, editors), 359-427 (1979), incorporated by reference herein. Techniques and compositions for making tablets (compressed and molded), capsules (hard and soft gelatin) and pills are described in Remington's Pharmaceutical Sciences (Arthur Osol, editor), 1553-1593 (1980), incorporated herein by reference.

In preparing the liquid oral dosage forms, the active component is incorporated into an aqueous-based orally acceptable pharmaceutical carrier consistent with conventional pharmaceutical practices. An "aqueous-based orally acceptable pharmaceutical carrier" is one wherein the entire or predominant solvent content is water. Typical carriers include simple aqueous solutions, syrups, dispersions and suspensions, and aqueous based emulsions such as the oil-in-water type. The most preferred carrier is a suspension of the pharmaceutical composition in an aqueous vehicle containing a suitable suspending agent. Suitable suspending agents include

Avicel RC-591 (a microcrystalline cellulose/sodium carboxymethyl cellulose mixture available from FMC), guar gum and the like. Such suspending agents are well known to those skilled in the art. While the amount of water in the compositions of this invention can vary over quite a wide range depending upon the total weight and  
5 volume of the active component and other optional non-active ingredients, the total water content, based on the weight of the final composition, will generally range from 2 about 20 to about 75%, and, preferably, from about 20 to about 40%, by weight/volume.

Although water itself may make up the entire carrier, typical liquid formulations preferably contain a co-solvent, for example, propylene glycol, glycerin, sorbitol solution and the like, to assist solubilization and incorporation of water-insoluble ingredients, such as flavoring oils and the like into the composition. In general, therefore, the compositions of this invention preferably contain from  
10 about 5 to about 25 volume/volume percent and, most preferably, from about 10 to about 20 volume/ volume percent, of the co-solvent.

The compositions of this invention may optionally contain one or more other known therapeutic agents, particularly those commonly utilized in cough/cold preparations, such as, for example, a cough suppressant such as dextromethorphan, chlorphedianol, carbapentane, caramiphen, noscapine, diphenhydramine, codeine,  
20 hydrocodone, hydromorphone, fominoben, their pharmaceutically-acceptable salts; an expectorant or mucolytic such as glyceryl guaiacolate, terpin, ammonium chloride, N-acetylcysteine and bromhexine, ambroxol, their pharmaceutically acceptable salts; and an antihistamine such as chlorpheniramine brompheniramine, dexchlorpheniramine, dexbrompheniramine, triprolidine, doxylamine,  
25 tripeleminamine, cyproheptadine, carbinoxamine, bromodiphenhydramine, phenindamine, pyrilamine, azatadine, their pharmaceutically acceptable salts, as well as the non-sedating antihistamines which include acrivastine, AHR-11325, phenindamine, astemizole, azelastine, cetirizine, ebastine, ketotifen, lodoxamide, loratidine, levocabastine, mequitazine, oxatomide, setastine, tazifylline, temelastine,  
30 and terfenadine, their pharmaceutically acceptable salts: all of these components, as well as their acceptable dosage ranges are described in the following: U.S. Patent 4,783,465 to Sunshine et al., issued November 8, 1988, U.S. Patent 4,619,934 to Sunshine et al., issued October 28, 1986, which are incorporated by reference herein. Also useful are bronchodilators such as theophylline and albuterol as well as  
35 other analgesic agents such as acetaminophen and aspirin. A highly preferred optional component is caffeine, which is preferably present at a level of from about 10% to about 50%.



Other optional ingredients well known to the pharmacist's art may also be included in amounts generally known for these ingredients, for example, natural or artificial sweeteners, flavoring agents, colorants and the like to provide a palatable and pleasant looking final product, antioxidants, for example, butylated hydroxy anisole or butylated hydroxy toluene, and preservatives, for example, methyl or propyl paraben or sodium benzoate, to prolong and enhance shelf life.

#### METHOD OF TREATMENT

The amount of the pharmaceutical composition administered depends upon the percent of active ingredients within its formula, which is a function of the amount of the ibuprofen and caffeine and any optional components such as a decongestant, expectorant and/or antihistamine required per dose, stability, release characteristics and other pharmaceutical parameters.

Usually from about 1 mg/kg to about 50 mg/kg per day, preferably from about 2 mg/kg to about 30 mg/kg per day and most preferably from about 3 mg/kg per day to about 20 mg/kg per day of the pharmaceutical composition is administered as described herein. This amount can be given in a single dose, or, preferably, in multiple (two to six) doses repeatedly or sustained release dosages over the course of treatment. Generally, each individual dosage of the pharmaceutical compositions of the present invention range from about 1 mg/kg to about 25 mg/kg, preferably from about 2 mg/kg to about 15 mg/kg and most preferably from about 3 mg/kg to about 10 mg/kg. Typical unit dosage forms for oral administration generally comprise from about 50 mg to about 2000 mg, preferably from about 100 mg to about 600 mg and most preferably from about 100 mg to about 400 mg of the ibuprofen and from about 25 mg to about 200 mg, preferably from about 50 mg to about 200 mg and most preferably from about 50 mg to about 100 mg of caffeine. While dosages higher than the foregoing are effective to provide analgesic relief, care must be taken, as with any drug, in some individuals to prevent adverse side effects.

The following examples illustrate embodiments of the subject invention wherein both essential and optional ingredients are combined.

#### EXAMPLE I

A hard gelatin capsule composition for oral administration is prepared by combining the following ingredients:

	<u>Ingredient</u>	<u>Amount</u>
35	Ibuprofen Lysinate	200 mg
	Caffeine	100 mg

Triturate active ingredients and q.s. with lactose to selected capsule size.

Administration of 1 or 2 of the above capsules to a human in need of treatment provides improved analgesic and/or anti-inflammatory effect.

#### EXAMPLE II

5 A hard gelatin capsule composition for oral administration is prepared by combining the following ingredients:

	<u>Ingredient</u>	<u>Amount</u>
	Naproxen Lysinate	200 mg
	Astemizole	5 mg
10	Caffeine	50 mg
	Glyceryl guaiacolate	100 mg

Triturate active ingredients and q.s. with lactose to selected capsule size.

Administration of 1 or 2 of the above capsules to a human in need of treatment provides improved analgesic and/or anti-inflammatory effect.

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#### EXAMPLE III

A liquid composition for oral administration is prepared by combining the following ingredients:

	<u>Ingredient</u>	<u>% W/V</u>
	Ketoprofen Lysinate	1.00
20	Caffeine	1.00
	Alcohol (95%)	25.000
	Propylene Glycol	25.000
	Sodium Citrate	2.000
	Citric Acid	0.250
25	Liquid Sugar (Simple Syrup)	25.00
	Glycerin	7.000
	Colorants	0.008
	Flavor	0.500
	Water, Purified QS	100.000

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The purified water (approximately 10% of the final batch volume) is poured into a batch container equipped with a lightnin' mixer. The sodium citrate, citric acid and Caffeine are added sequentially and dissolved with agitation. The glycerin and liquid sugar are then colorants added. In a separate container the colorants are added to purified water (approximately 0.5% of the final batch volume). This colorant solution is then added to the first batch container. In a separate container the Ketoprofen lysinate is added to the alcohol while stirring. The propylene glycol and flavors are added to this alcohol premix and the resulting mixture is stirred until

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homogeneous and then added to the first container. The remaining purified water is added to the resulting mixture and stirred.

Administration of 10 ml to 20 ml (2 to 4 teaspoonsful) to a human in need of treatment provides improved analgesic and/or anti-inflammatory effect.

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#### EXAMPLE IV

A liquid composition for oral administration is prepared by combining the following ingredients:

	<u>Ingredient</u>	<u>% W/V</u>
	Ibuprofen Arginate	1.00
10	Caffeine	1.00
	Chlorpheniramine Maleate	0.02
	Pseudoephedrine HCl	0.30
	Alcohol (95%)	25.00
	Propylene Glycol	25.00
15	Sodium Citrate	2.00
	Citric Acid	0.25
	Liquid Sugar (Simple Syrup)	25.00
	Glycerin	7.00
	Colorants	0.008
20	Flavor	0.50
	Water, Purified QS	100.00

The purified water (approximately 10% of the final batch volume) is poured into a batch container equipped with a lightnin' mixer. The sodium citrate, citric acid, pseudoephedrine HCl and chlorpheniramine maleate are added sequentially and dissolved with agitation. The glycerin and liquid sugar are then added. In a separate container the colorants are added to purified water (approximately 0.5% of the final batch volume). This colorant solution is then added to the first batch container. In a separate container the ibuprofen arginate is added to the alcohol while stirring. The propylene glycol and flavors are added to this alcohol premix and the resulting mixture is stirred until homogeneous and then added to the first container. The remaining purified water is added to the resulting mixture and stirred.

Administration of 10 ml to 20 ml (2 to 4 Teaspoonsful) to a human in need of treatment provides improved analgesic and/or anti-inflammatory effect.

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#### EXAMPLE V

A liquid composition for oral administration is prepared by combining the following ingredients:

	<u>Ingredient</u>	<u>% W/V</u>
	S(+)-Ibuprofen Lysinate	1.00
	Caffeine	1.00
	Pseudoephedrine HCl	0.30
5	Chlorpheniramine Maleate	0.02
	Dextromethorphan HBr	0.15
	Alcohol (95%)	25.00
	Propylene Glycol	25.00
	Sodium Citrate	2.00
10	Citric Acid	0.25
	Liquid Sugar (Simple Syrup)	25.00
	Glycerin	7.00
	Colorants	0.008
	Flavor	0.50
15	Water, Purified QS	100.00

The purified water (approximately 10% of the final batch volume) is poured into a batch container equipped with a lightnin' mixer. The sodium citrate, citric acid, pseudoephedrine HCl and chlorpheniramine maleate are added sequentially and dissolved with agitation. The glycerin and liquid sugar are then added. In a separate container the colorants are added to purified water (approximately 0.5% of the final batch volume). This colorant solution is then added to the first batch container. In a separate container the (S) + ibuprofen lysinate and dextromethorphan HBr are added sequentially to the alcohol while stirring.

The propylene glycol and flavors are added to this alcohol premix and the resulting mixture is stirred until homogeneous and then added to the first container. The remaining purified water is added to the resulting mixture and stirred.

Administration of 10 ml to 20 ml (2 to 4 teaspoonsful) to a human in need of treatment provides improved analgesic and/or anti-inflammatory effect.

What is Claimed is:

1. A pharmaceutical composition adapted to elicit an onset-hastened and enhanced analgesic response in a mammalian organism in need of such treatment and adapted for unit dosage administration, said composition comprising:
  - a. an analgesically and anti-inflammatory effective amount of amino acid salt of a propionic acid nonsteroidal anti-inflammatory agent; and
  - b. an amount of caffeine sufficient to hasten the onset of and enhance the analgesic response.
2. A pharmaceutical composition according to Claim 1 wherein said propionic acid derivative is selected from the group consisting of ibuprofen, naproxen, benoxaprofen, flurbiprofen, ketoprofen, fenoprofen, fenbufen, indoprofen, piroprofen, carprofen, oxaprozin, pranoprofen, miroprofen, tioxaprofen, suprofen, alminoprofen, and tiaprofen preferably, wherein said propionic acid derivative is selected from the group consisting of ibuprofen, naproxen, flurbiprofen, ketoprofen, fenoprofen, indoprofen, piroprofen and wherein said amino acid salt is selected from the group consisting of triethylamine, tripropylamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, lysine, ornithine, arginine, histidine, caffeine, procaine, N-ethylpiperidine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglycamine, theobromine, purine, piperazine and piperidine and mixtures thereof.
3. A pharmaceutical composition according to any of the preceding Claims comprising from 20 to 200 mg caffeine, preferably comprising from 32 to 150 mg caffeine, and more preferably comprising from 32 to 100 mg caffeine.
4. A pharmaceutical composition according to any of the preceding Claims wherein said amino acid salt is selected from the group consisting of lysine, ornithine and arginine and mixtures thereof.
5. A pharmaceutical composition according to any of the preceding Claims which comprises the S(+) enantiomer of the amino acid salt of a propionic acid nonsteroidal anti-inflammatory agent.

6. A pharmaceutical composition according to any of the preceding Claims comprising from 5 to 75 mg S(+)-ketoprofen lysinate.
7. A pharmaceutical composition according to any of Claims 1 through 5 comprising from 50 to 800 mg S(+)-ibuprofen lysinate.
8. A pharmaceutical composition according to any of Claims 1 through 5 comprising from 50 to 800 mg S(+)-naproxen lysinate.
9. A pharmaceutical composition according to any of the preceding Claims wherein said pharmaceutical composition further comprises at least one other active component selected from the group consisting of an antihistamine, cough suppressant and expectorant and mixtures thereof.
10. A method for providing improved analgesic and/or anti-inflammatory relief by administering a safe and effective amount of the composition of any of the preceding Claims.

## INTERNATIONAL SEARCH REPORT

Intern. Application No  
PCT/US 94/09582

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 A61K31/52 //(A61K31/52,31:19)

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO,A,94 07471 (MERCK &CO., INC) 14 April 1994 see abstract see page 3, line 12-16 ---	1-5,7
X,P	WO,A,94 16703 (MERCK & CO., INC) 4 August 1994 see page 2, line 19 - line 24 ---	1,7
X,P	WO,A,94 14449 (THE PROCTER & GAMBLE COMPANY) 7 July 1994 see page 5, line 21-34 see claims 1-5 ---	1-7,9,10
Y	EP,A,0 136 470 (MERCKLE GMBH) 10 April 1985 see abstract ---	1-3
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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